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MOLECULAR DOCKING OF FRUCTOSE-DERIVED NUCLEOSIDE ANALOGS AGAINST REVERSE TRANSCRIPTASE OF HIV-1

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ABSTRACT

AIDS is a chronic infection that compromises the immune system of the individual infected with HIV. HIV is a retrovirus, that is, it has RNA as a genetic material, and needs the action of reverse transcriptase (RT) to multiply. A nucleoside is formed by the bond between a carbohydrate and a nitrogenous base that is inserted into the genetic material preventing multiplication. This work consists of a computational analysis through Molecular Docking in order to predict the potential inhibitory activity of RT from a series of 24 nucleoside analogs derived from fructopyranose compared to the bioactive molecules already inserted in the anti-HIV treatment. For this study 36 molecules were designed in ChemDraw Ultra 12.0 to obtain its 2D structural formula. Then the molecule was optimized MM + and AM1 using HyperChemTM (Release 8.0.6 for Windows). Finally, the enzyme RT in PBD (PDB ID 1REV) was selected and in Molegro Virtual Docking 6.0 anchorage was performed. It is possible to conclude that some molecules presented favorable energies for the formation of the ligand-enzyme complexes, as well as the presence of interactions with amino acid residues common to known inhibitors.

Keywords: nucleosides, HIV, reverse transcriptase, molecular modeling, virtual screening, *in silico*.

INTRODUCTION

AIDS is still considered a pandemic, considered as a global public health problem that has contributed to the deaths of 35 million people infected, with 1 million deaths occurring in 2016 as victims of HIV-related immunodeficiency. According to the World Health Organization (WHO) survey in 2016 there were 36.7 million infected, of whom 1.8 million were infected in the same year of the survey. (WHO, 2018a; France, 2016)

The demographic distribution WHO (2018a) of those infected by HIV shows that 69.83% of the cases are distributed on the African continent, followed by 9.55% in Southeast Asia and 9.00% in the American continent.

HIV is a virus of the family Retroviridae, a family of viruses whose genome is formed by a single strand of RNA and its parasitological life cycle begins by the synthesis of its DNA from its own viral RNA, through the enzyme reverse transcriptase (RT). Continuing the HIV taxonomy, it is within the lentivirus genre in which viruses with high incubation times are present, and the infected individual can spend long periods with the virus asymptomatically in the body. It is worth noting that lentiviruses have an ability to replicate, giving greater speed to the evolution to an infectious disease (Acquired Immunodeficiency Syndrome - AIDS). (Sanjuán & Bordería, 2010; Mustanski, Newcomb, Du Bois, Garcia & Grov, 2011; Jiang Et Al., 2010; Siqueira, 2012)

One of the therapeutic alternatives commonly used in retroviral treatment is the use of nucleoside analogues to inhibit the action of RT (France, 2016; Nunes, Caliani, Nunes & Mello, 2015). Nucleoside analogs are not differentiable from the natural nucleosides by the enzyme, where these once incorporated analogs do not are recognized and prevents clustering in the natural nucleotides, thus, the entire viral multiplication process is terminated.

According to several studies, retroviral anti-HIV treatment can be classified into 3 distinct pharmacological forms of action with their chronological order in the treatment history of those infected: in 1991 the nucleoside RT inhibitors, 1995 the protease inhibitors and in 1996 the non-nucleoside inhibitors of RT (Nunes, Caliani, Nunes & Mello, 2015; Novotny, Hendrickson, Soares, Sereno, & Kiene, 2017; Bittencourt et al., 2015). The Food and Drug Administration (FDA) also adds integrase inhibitors, fusion inhibitors and CCR5 inhibitors (Lozano et al., 2012). Thus, after insertion of these drugs, it was possible to perceive the decrease in the mortality of HIV-infected individuals.

One of the strategies used today in modern medical chemistry is the insertion of computational methods for the planning of new drugs (Veljkovic, 2006; Guido, Andricopulo & Oliva, 2010; Lima, 207). Through *in silico* methods it is possible to perform a screening by analyzing some important aspects for the promotion of a drug bioactive, such as anchoring with the target (molecule-receptor system), toxicity and metabolism of the substance, thereby selecting molecules with better profile with promising pharmacodynamic and pharmacokinetic properties. (Jónsdóttir, Jorgensen & Brunak, 2005; 15; Miller et al., 2017; Andricopulo & Montanari, 2005)

Zidovudine (AZT), Figure 01, was the first drug synthesized in 1964 to be used in anti-HIV treatment (Fischl et al., 1987), this substance has the function of inhibiting the action of the enzyme that performs viral DNA synthesis when the virus parasite the cell. This drug reduces up to 80% the presence of opportunistic diseases in seropositive patients and up to 50% the deaths caused by secondary diseases. (France, 2016; Nunes et al., 2015; Fischl et al., 1987; Horwitz, Chua & Noel, 1964)

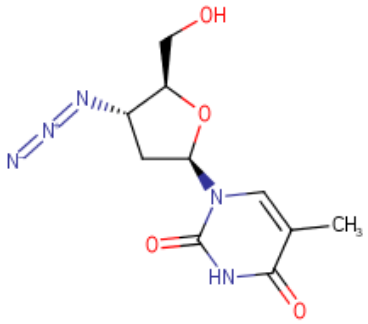


Figure 01. Structure 2D of zidovudine (AZT).

For this study, *in silico* studies were performed through the Molecular Docking to know the energy of interaction with the specific receptor, involving the inhibition of RT. With this screening, it is possible to select molecules with anti-HIV profile, derived from the fructospermine, taking as a positive control the molecule of AZT. These data may be used to propose nucleoside analogs from those identified in this screening with improved biological activity.

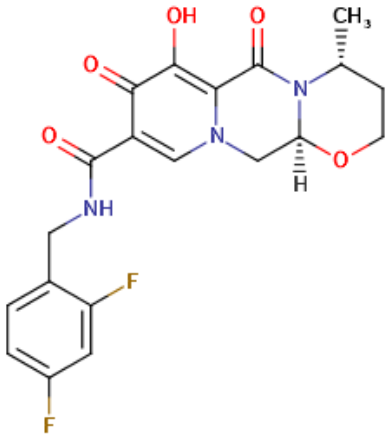


Figure 02. Structure Dolutegravir (DTG) 2D.

The importance of studies in this area is due to the great toxicity that bioactive molecules with anti-HIV profile present against normal cells, especially hepatic, neural and gastric cells, considering that the bioactive drugs used in the treatment of AIDS also have activity against non-specific enzymes such as protease and integrase, both enzymes present in healthy cells. Recently the WHO published an alert about the risks that the use of dolutegravir - DTG (Figure 02) at conception can offer to the neural tube of the fetus. (WHO, 2018b)

A nucleoside is formed by the union of a carbohydrate and a nitrogenous base, commonly using pentoses and deoxypentoses, in which the *N*-glycosidic covalent bond is formed commonly between N^{9}_{base}-$C^{1}_{carbohydrate}$ in the purine bases and N^{1}_{base}-$C^{1}_{carbohydrate}$ in the pyrimidine bases . (France, 2016; Champe, Harvey & Ferrier, 2011; Nelson, 2002)

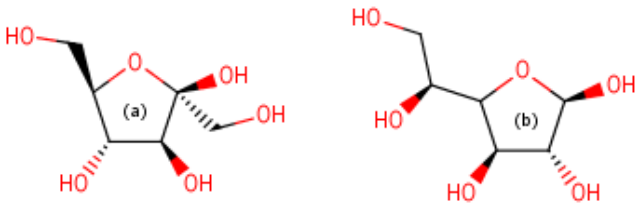


Figure 03. Structure 2D of β-fructofuranose (a) and β-glucofuranose (b)

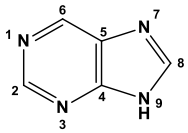
The fructose (Figure 03a) is a monosaccharide very abundant in the human body (Barreiros, Bossolan & Trindade, 2005), which is also present in fruits, its consumption is recommended to patients with a high glycemic rate, in the control of diabetes, since it has a chemical structure similar to glucose (Figure 03b) and a very pronounced sweet taste (Oliveira & Marchini, 2008), however the great difference between these two carbohydrates lies in their distinct metabolisms, since glucose requires insulin.

MATERIAL OF METHOD

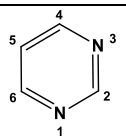
In this work a virtual screening of 24 nucleosides (Table 01) derived from β-fructofuranose with different nitrogenous, purine and pyrimidine bases was performed, together with 12 molecules of drugs already used in anti-HIV treatment, to identify the best profile of the studied series. And the interactions between amino acid residues common to better profile molecules.

Initially all these molecules had their structures optimized by two methods, then the Molecular Docking was performed using a protein from the PDB (Protein Data Bank - https://www.rcsb.org), referring to the TR, after the anchorage to best pose for each molecule was chosen according to the corresponding MolDock Score values.

Table 01. Compounds used in the research.



Purines



Pirimidines

Cod.	Compound	PM	Cód.	Compound	PM
ALX01	Abacavir	300.359	ALX19	Indinavir	613.789
ALX02	Adefovir	273.186	ALX20	N^3-(orotine acid)-R	318.237
ALX03	N^9-adenine-R	297.267	ALX21	N^1,N^3-(orotine acid)-di-R	480.377
ALX04	AZT	267.241	ALX22	N^1-(orotine acid)-R	318.237
ALX05	N^1-barbiturine-R	290.227	ALX23	N^3-paraxantine-R	342.305
ALX06	N^1,N^3-barbiturine-di-R	452.367	ALX24	Telbuvudina	242.229
ALX07	Cidofovir	279.187	ALX25	Tenofovir	287.212
ALX08	N^1-citosine-R	273.243	ALX26	N^1-teobromina-R	342.305
ALX09	Didanosina	236.227	ALX27	N^9-teofiline-R	342.305
ALX10	Efavirez	315.675	ALX28	N^1-timine-R	288.254
ALX11	Emtricitabina	247.247	ALX29	N^1-uracine-R	274.227
ALX12	Entecavir	277.279	ALX30	N^9-(urine acid)-R	330.251
ALX13	Estavudina	224.213	ALX31	N^7-(urine acid)-R	330.251
ALX14	Fructose	292.218	ALX32	N^1-(urine acid)-R	330.251
ALX15	N^1-(F-uracine)-R	180.156	ALX33	N^3-(urine acid)-R	330.251

ALX16	N^9-guanine-R	313.267	ALX34	N^9-xantine-R	314.251
ALX17	N^9-hipoxantine-R	298.252	ALX35	N^3-xantine-R	314.251
ALX18	N^1-hipoxantine-R	298.252	ALX36	N^1-xantine-R	314.251

Molecular Weight - [PM] = g.mol-1

β-fructofuranoside-R

For better discussion it is convenient to calculate two pharmacodynamic and pharmacokinetic parameters as the absorption rate (% ABS) (Silva et al., 2015; Oliveira et al., 2012; Peixoto et al., 2016) and the inhibitory constant (K_i), through the following equations:

$$\%ABS = 109-(0.3345xTPSA) \quad \text{Equation 01}$$

$$\Delta G = -RTlnK_i \quad \text{Equation 02}$$

Thus, the prediction of these two parameters may contribute to the selection of the molecules with better prototypical biological profiles to drugs, for this it is necessary to predict the Polar Topological Surface Area (TPSA) (Ertl, Rohde & Selzer, 2000; Fernandes & Gattass, 2009; Schaftenaar & Vlieg, 2012; Jarrahpour et al., 2012; Jarrahpour et al., 2010; Lahsasni et al., 2014; Hou, Zhang, Xia, Qiao & Xu, 2004), in this research this prediction was performed through of the free Molinspiration® online application (Bratislava University, 2017). The inhibition constant was calculated from the anchoring energies obtained in the molecular docking, where R is the general constant of the perfect gases and T is the temperature.

Molecular Docking

Initially the molecules were designed in their 2D form in the ChemDraw Ultra 12.0 program (Berić, Jelić, Nešić, Trbojević-Stanković & Odović, 2017), for the anchorage study (ligand-receptor) initially all the molecules had their energy minimized in the search of the lower energy conformation (RMS 0.1 Kcal / Å (MM +) (Allinger, 1977). The algorithm was developed using the HyperChemTM (Release 8.0.6 for Windows) software, using the force field of molecular mechanics (MM +) (Allinger, 1977) and the semi-empirical (AM1) (Dewar, Zoebisch, Healy & Stewart, 1985). The target chosen for this research was the PDB ID (Berman et al., 2000) 1REV (Ren et al., 1995), because it corresponds to an enzyme protein to be inhibited, once chosen, the target was imported into the software Molegro Virtual Docking 6.0 (MVD) to realize the template selecting the appropriate interaction site, after all, molecular anchoring was started.

Qualitative prediction of toxicity

In addition to the anchoring with the chosen receptor, a qualitative *in silico* study was performed to predict the toxicity of each compound, making it a parameter of selection of structures with good anti-HIV pharmacological profiles. Knowing that these compounds have affinity for other

active sites in several targets already mentioned, the toxicity becomes a fundamental parameter for the election of a bioactive to drug. For this study we used the free Vega QSAR software (see 1.1.3 build date: 19/09/2016) (Ghorbanzadeh, Zhang & Andersson Patrik, 2016; Benfenati, Manganaro & Gini, 2013; Golbamaki et al., 2014; Pizzo, Lombardo, Manganaro & Benfenati, 2013) developed in the Java® for Windows programming language.

RESULTS AND DISCUSSION

Molecular Docking

According to the energetic data obtained in the molecular docking (Souza, 2012; Simonetti et al., 2017; Almeida, 2018; Oliveira et al., 2008; Cardoso, Moraes & Cass, 2009; Soares, 2011; Foresto et al., 2017) (Table 02) correlating with the structures of 12 drugs used in the treatment of seropositive, among the structures of the nucleoside analogues studied, only two had low affinity for the binding site (ALX05 and ALX015).

Table 02. Values obtained after molecular anchoring.

Cod.	MolDock Score	Cod.	MolDock Score
ALX01	-117.9960	ALX19	-178.2620
ALX02	-97.7808	ALX20	-91.9244
ALX03	-98.2466	ALX21	-103.0860
ALX04	-96.1751	ALX22	-85.0810
ALX05	-61.9241	ALX23	-81.4854
ALX06	-100.4870	ALX24	-84.5389
ALX07	-93.1448	ALX25	-101.9030
ALX08	-80.2223	ALX26	-76.8097
ALX09	-85.5961	ALX27	-92.1091
ALX10	-104.8640	ALX28	-81.8189
ALX11	-75.6019	ALX29	-85.0627
ALX12	-103.0430	ALX30	-105.8900
ALX13	-71.6477	ALX31	-102.3530
ALX14	-88.6736	ALX32	-93.9533
ALX15	-51.2576	ALX33	-88.9166
ALX16	-104.0450	ALX34	-100.7800
ALX17	-94.9336	ALX35	-83.2611
ALX18	-77.3818	ALX36	-76.9175

The analysis of the MolDock Score reveals that 22 nucleoside analogs studied presented better results than the drugs Emtricitabine and Stavudine, that 15 compounds had better results than Telbivudine, 13 were better than Didanosine and that 1 compound had a better result than 10 (out of 12) bioactive drugs present in anti-HIV drugs, as shown in the bar chart in Figure 04:

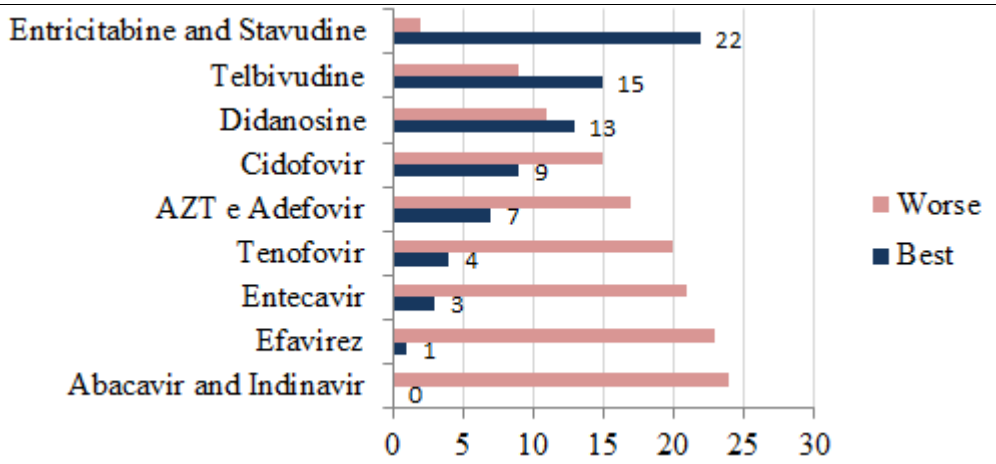


Figure 04. Relationship between analogs and selected drugs.

The analogue that showed the best interaction with the chosen target was the compound with code ALX30, which corresponds to a fructofuranose bound by anomeric carbon with the N^9 atom of uric acid, through a *β*-*N*-glycosidic bond (Figure 05).

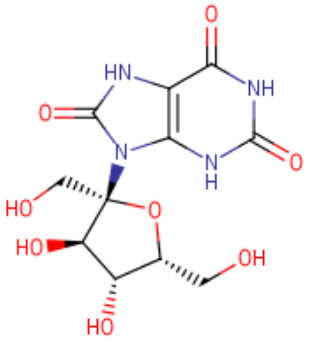
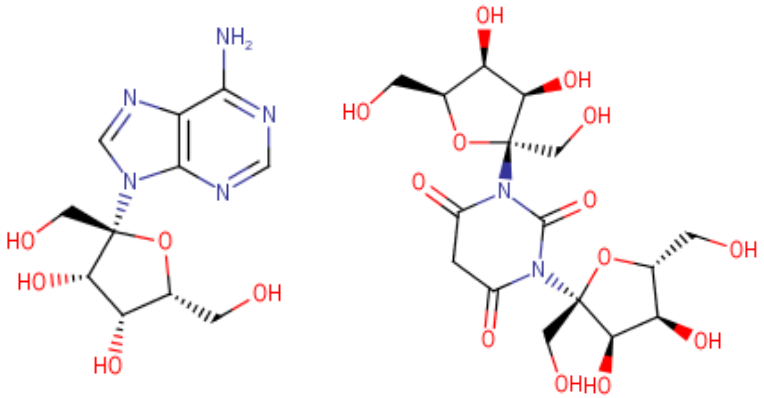
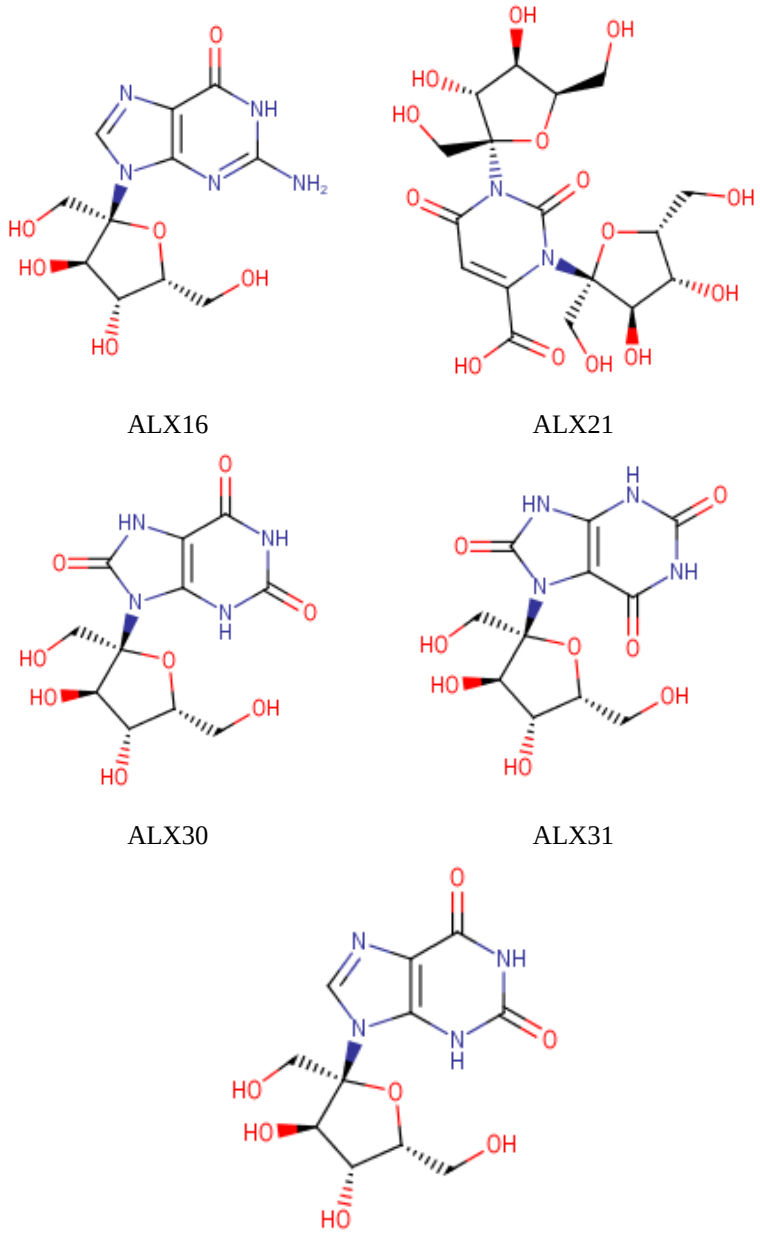


Figure 05. Structure 2D of compound ALX30.

Among the analogues studied in this research, it is relevant to highlight the molecules ALX16, ALX21, ALX30 and ALX31, as they presented better anchorage results than Tenofovir, a drug used in the 3 in 1 treatment adopted in Brazil, which consists in the administration of 1 tablet containing Tenofovir + Lamivudine + Efavirez (Foresto et al., 2017; Santos, Secoli & Padoin, 2016; Barros & Vieira-da-Silva, 2017; Silva, Dourado, Brito & Silva, 2015). AZT is a drug approved since 1987 by the FDA (Fischl, 1987) used in the treatment of HIV-positive seropositive patients and since 1990 has been incorporated into the Pre-Exposure Prophylaxis (PRPE) preventive treatment, according to data obtained from molecular docking in this ALX06, ALX16, ALX21, ALX30, ALX31 and ALX34 showed promising MolDock Score results for the inhibition of RT (Figure 06).



ALX03 ALX06



ALX16 ALX21

ALX30 ALX31

ALX34

Figure 06. Molecules with better anchoring energies than AZT.

Absorption Rate and Inhibitory Constant

For the investigational study of the potentiality of a compound as a drug candidate it is necessary to discuss the rate of absorption of the bioactive (% ABS), TPSA data were essential for the prediction of% ABS (Costa et al., 2016; Singh, Sharma, Mishra, Pandiya & Kumar, 2017; Singh, Gupta & Verma, 2013; Singh & Singh, 2011), 22 The compounds of the present invention have a value of between 40% and 100%: ALX03, ALX08, ALX14, ALX14, ALX15, ALX16, ALX17, ALX18, ALX20, ALX22, ALX22, ALX23, ALX26, ALX28, ALX28, ALX29, ALX30, ALX31, ALX35 and ALX36, as shown in the bar graph in Figure 07:

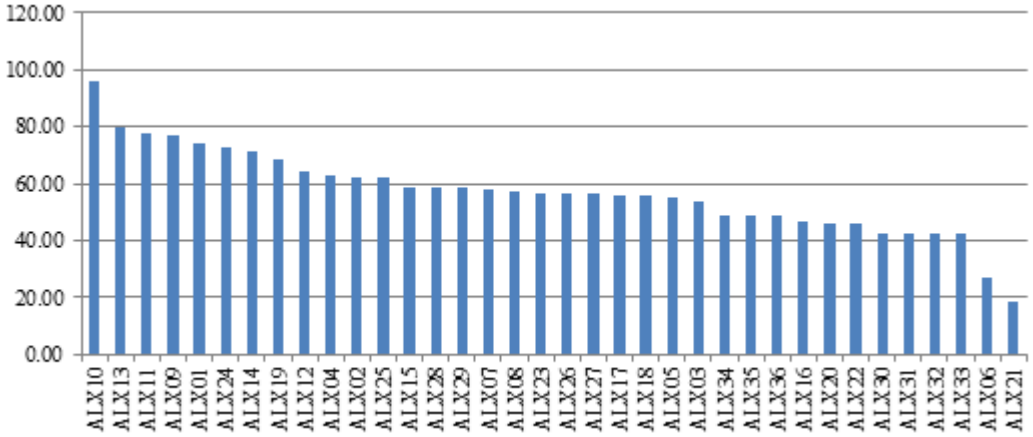


Figure 07. Relationship of compounds based on% ABS.

Comparing the relation of the compounds classified by the absorption rate with the compounds that presented the best results in molecular docking, it is possible to highlight five compounds that presented satisfactory results in both chemoinformatic analyzes: ALX03, ALX16, ALX30, ALX31 and ALX34.

Another important parameter besides the absorption rate is the inhibitory constant (K_i), with which it is possible to classify the compounds as to the degree of receptor-ligand affinity, according to the data presented in Table 04 concerning the predictions of some properties relevant for In this study (Equation 02), we can see the K_i values that the compound ALX03 presented better interactions among the 5 compounds selected by the two previous analyzes (Table 03).

Table 03. Prediction values of some properties.

Cod.	K_i	miLogP	HBA	HBD	TPSA	%ABS
ALX01	1.0488	1.47	07	04	101.89	73.85
ALX02	1.0402	-0.98	09	04	136.39	61.95
ALX03	1.0404	-1.42	10	06	159.78	53.88
ALX04	1.0396	-0.10	09	02	134.08	62.74
ALX05	1.0253	-2.40	10	05	156.62	54.97
ALX06	1.0414	-4.35	15	08	237.98	26.90
ALX07	1.0383	-2.70	09	05	147.91	57.97
ALX08	1.0329	-2.49	09	06	151.07	56.88
ALX09	1.0351	-0.95	07	02	93.04	76.90
ALX10	1.0432	4.53	03	01	38.33	95.78
ALX11	1.0310	-0.67	06	03	90.38	77.82
ALX12	1.0424	-1.06	08	05	130.06	64.13
ALX13	1.0293	-0.54	06	02	84.33	79.91
ALX14	1.0209	-2.04	06	05	110.37	70.92
ALX15	1.0364	-2.24	09	05	145.01	58.97
ALX16	1.0429	-2.58	11	07	179.75	46.99
ALX17	1.0390	-2.38	10	05	153.73	55.96
ALX18	1.0317	-1.44	10	05	153.73	55.96
ALX19	1.0746	2.51	09	04	118.02	68.28
ALX20	1.0378	-2.52	11	06	182.31	46.10

ALX21	1.0425	-4.16	16	09	261.60	18.75
ALX22	1.0349	-2.52	11	06	182.31	46.10
ALX23	1.0334	-1.66	11	04	151.98	56.57
ALX24	1.0347	-1.43	07	03	104.56	72.93
ALX25	1.0420	-0.62	09	04	136.39	61.95
ALX26	1.0315	-1.66	11	04	151.98	56.57
ALX27	1.0379	-1.66	11	04	151.98	56.57
ALX28	1.0336	-1.95	09	05	145.01	58.97
ALX29	1.0349	-2.65	09	05	145.01	58.97
ALX30	1.0436	-3.09	12	07	193.67	42.18
ALX31	1.0422	-3.09	12	07	193.67	42.18
ALX32	1.0386	-2.15	12	07	193.67	42.18
ALX33	1.0365	-3.09	12	07	193.67	42.18
ALX34	1.0415	-2.74	11	06	173.70	49.07
ALX35	1.0342	-2.74	11	06	173.70	49.07
ALX36	1.0315	-1.79	11	06	173.70	49.07

HBA - Hydrogen Binding Acceptors; HBD - Hydrogen Binding Donors; Log P - Partition Coefficient (Octanol / Water); Ki - Inhibitory Constant.

Qualitative prediction of toxicity

A qualitative toxicity prediction was made in order to further restrict the relationship of promising structures to anti-HIV drugs, initially in this study the nature of the toxicity and its toxic action mechanism were not considered, only to know their relative toxicity (Price & Chaudhry, 2014; Benfenati, Manganaro & Gini, 2013; Mombelli, Raitano & Benfenati, 2016; Veljkovic et al., 2015). Desiring the Boolean results obtained, the compounds ALX03 and ALX16 presented toxicity, but the compounds ALX30, ALX31 and ALX34 do not present any apparent relative toxicity according to the software used for this *in silico* screening. All results for each sample can be seen in Frame 01 along with the reliability of each prediction.

Frame 01. Qualitative analysis on general toxicity.

Cod.	Reab.	Toxidade	Cod.	Reab.	Toxidade
ALX01	Low	Yes	ALX19	Low	No
ALX02	Low	Yes	ALX20	Low	No
ALX03	Low	Yes	ALX21	Low	No
ALX04	Low	Yes	ALX22	Low	No
ALX05	Low	No	ALX23	Low	No
ALX06	Low	No	ALX24	Moderate	No
ALX07	Low	Yes	ALX25	Low	Yes
ALX08	Low	Yes	ALX26	Low	No
ALX09	Low	Yes	ALX27	Low	Yes

ALX10	Low	No	ALX28	Low	Yes
ALX11	Low	Yes	ALX29	Low	Yes
ALX12	Low	No	ALX30	Low	No
ALX13	Good	Yes	ALX31	Low	No
ALX14	Moderate	No	ALX32	Low	No
ALX15	Low	No	ALX33	Low	No
ALX16	Low	Yes	ALX34	Low	No
ALX17	Low	Yes	ALX35	Low	Yes
ALX18	Low	Yes	ALX36	Low	Yes

Reab – Reability.

Analysis of amino acid residues on the linker-receptor interaction

This discussion brings about the existence of common interactions, all compounds showed interactions with similar residues, both the drugs and the nucleoside analogs studied: GLY190, LEU234, PHE227, PRO227, PRO236, TRY181, TYR188, VAL106, VAL179.

Residues TYR188, HIS235 and LYS101 were interacting with compounds ALX30, ALX31 and ALX34 through hydrogen bonds. In addition, the compounds showed a common amino acid residue with 9 of the drugs studied: TYR188, leading to the belief that these residues may influence the biological action of these compounds.

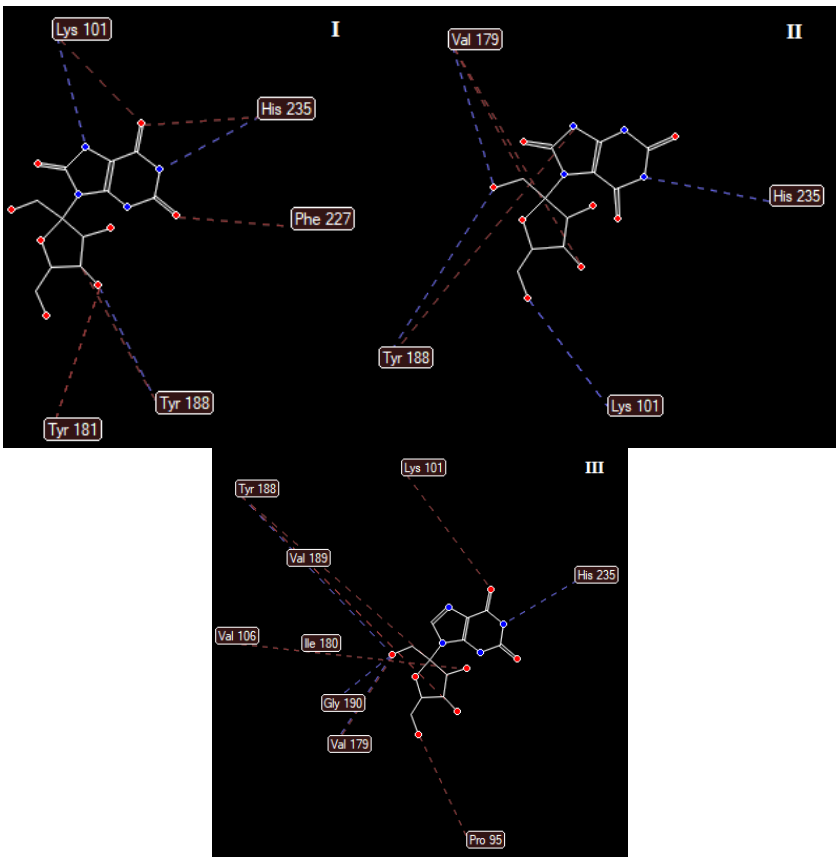


Figure 06. Interaction of ALX30 (I), ALX31 (II) and ALX34 (III) with the amino acid

residues of the 1REV target.

The compounds ALX30, ALX31 and ALX34 show interactions in 3 residues common among them and with the drugs selected in this research, as can be shown in Figure 06 where the blue dashed lines correspond to the hydrogen bonds and the red ones are steric interactions.

CONCLUSION

It may be concluded from the present work that fructose-derived nucleoside analogs may be bioactive anti-HIV promising, based on the data shown the compound which presented the best profile among the series worked in this study was compound ALX030, due to lower anchorage energy among the 3 compounds selected by screening (ALX30, ALX31 and ALX34), a compound formed by coupling between fructofuranosis and uric acid, an unpublished analog whose IUPAC name is 9 - [(2S, 3R, 4R, 5R) -3,4-dihydroxy-2,5-bis (hydroxymethyl)oxolan-2-yl]-2,3,6,7,8,9-hexahydro-1H-purine-2,6,8-trione and a molecular weight of 330,251 g.mol-1. However, the compounds ALX31 and ALX34 also presented primitive results.

With the prediction of some pharmacodynamic and pharmacokinetic properties as the inhibition constant and the rate of absorption as well as the qualitative toxicity it was possible to restrict the series to only one compound, which presented the 10th lower energy in the molecular docking, showed no toxicity .

The hydrogen bonds and steric interaction of compounds ALX30, ALX31 and ALX34 were present in the drugs used as reference, presenting greater similarity with Didanosine, Entecavir, Efavirez, Tenofovir, Emtricitabina and Indinavir. Important interactions could be the biological activity of the molecule that presented better profile in this screening.

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